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(54) Title: USE OF 5HT–6 ANTAGONISTS

(57) Abstract

The invention relates to the use of 5–HT6 receptor antagonists containing arylsulfamide or arylaminosulfonyl groups in the manufacture of a medicament for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

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USE OF 5HT-6 ANTAGONISTS

The present invention relates to the use of compounds known in the art as 5-HT_6 receptor antagonists in the treatment of hyperactivity disorders. More particularly the invention relates to the use of such compounds in the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Attention Deficit Hyperactivity Disorder, which is also referred to in the literature as Attention Deficit Disorder/Hyperactivity Syndrome (ADD/HS), is a condition (or group of conditions) characterised by impulsiveness, distractibility, inappropriate behaviour in social situations and hyperactivity. ADD/HS is reported to have a prevalence of 3-5% (using DSM-IV criteria) in children (Diagnostic and Statistical Manual of Mental Disorders; 4th edition; American Psychiatric Association; 1994). It is believed that some 30-60% of such cases persist into adulthood (Zametkin A. J. and Borcherding B.G., Ann. Rev. Med. 1989, 40:447-51). This disorder can impair social function, learning and/or development and is therefore now recognised as a serious problem. It is further recognised that many children with ADHD go on to develop other comorbid conditions or social problems in adulthood.

In clinical terms ADHD is diagnosed if any one of the three main clinical features viz. inattention, over-activity and impulsiveness, persists in two or more situations, e.g. in both a home and school environment (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Washington DC: American Psychiatric Association, 1994).

A particularly severe form of ADHD is termed Hyperkinetic Disorder. In Britain, this diagnosis is made only if all three of the main clinical features (inattention, over-activity and impulsiveness) have been present from an early age, persist in more than one situation (e.g. home and school) and impair function (The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. Geneva: World Health Organisation, 1993: 155-7). Reports indicate that 1 in 200 children suffer from hyperkinetic disorder (Taylor E., et al, The Epidemiology of Childhood Hyperactivity, Oxford University Press 1991: 93-113).

There are currently only a few therapeutic agents which are recognised as having efficacy in the treatment of childhood ADHD; at present the drugs of choice are dextroamphetamine, pemoline and in particular methylphenidate (Ritalin, TM). Antidepressants and antipsychotic medications such as risperidone may also be effective in some cases but these are not standard treatments. Although methylphenidate is probably the most widely used drug in the treatment of ADHD it suffers from a number of disadvantages: it is a controlled drug; is extensively metabolised and may cause

confusion and hallucinations. Moreover, methylphenidate does not treat one of the three main clinical features of ADHD, namely inattentiveness, and in addition does not normalise ADHD children. There is therefore a need for a new treatment for ADHD and related disorders which demonstrate both an improved pharmacological profile and which do not have the associated disadvantages of currently known therapeutic agents.

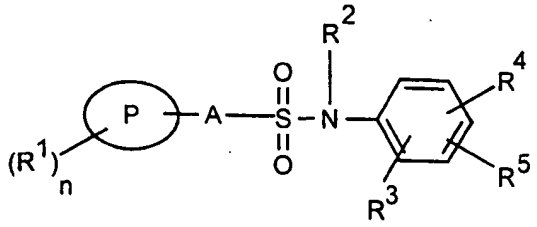
The etiology of ADHD is still not well understood. However, there is evidence to suggest that ADHD is associated with abnormalities in the caudate (Ernst et al, Journal of Neuroscience, 1998, 18(15), 5901-5907.). It has now been found that certain compounds, known in the art as 5-HT_6 receptor antagonists, selectively increases activity of the nigro-striatal dopamine pathway and could therefore, specifically alleviate these abnormalities. The compounds of the present invention have additional effects on the central nervous system, namely, an increase in cognitive function. Consequently, such compounds have utility in the treatment of ADHD and related disorders.

The present invention therefore provides, in a first aspect, the use of a compound having 5-HT_6 receptor antagonist activity in the manufacture of a medicament for use in the treatment of ADHD.

A 5-HT_6 antagonist for use in this invention must be selective for 5-HT_6 receptors. Where used herein, this is intended to mean that the 5-HT_6 antagonist must have a greater than 10-fold selectivity for this receptor over other binding sites within the CNS, in particular, other 5-HT receptor sub-types and dopaminergic receptors. The most preferred compounds of this invention demonstrate greater than 100-fold selectivity for 5-HT_6 receptors. The selectivity of the compounds of this invention for 5-HT_6 receptors can be determined using binding assays methods which are well known to those skilled in the art.

Preferred compounds of this invention include those disclosed in patent applications WO 98/27081 (SmithKline Beecham p.l.c.) and WO 99/02502 (SmithKline Beecham p.l.c.). Compounds of this invention therefore include compounds of formula (A) and compounds of formula (B), which can be prepared according to methods described in WO 98/27081 and WO 99/02502 respectively.

Compounds of Formula (A)



(A)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6,

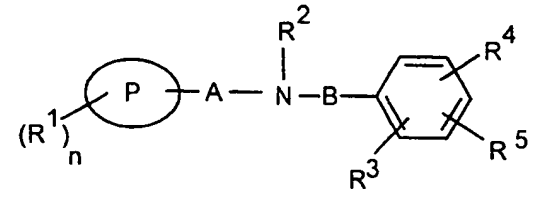
R^2 is hydrogen, C_{1-6} alkyl or arylC_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N- C_{1-6} alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl.

Compounds of Formula (B)



(B)

wherein:

P is phenyl, naphthyl, anthracenyl, a bicyclic heterocyclic ring, a tricyclic heteroaromatic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

B is SO_2;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more fluorine atoms, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, nitro, cyano, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6}alkyl or optionally substituted phenyl, SR^{11} where R^{11} is as defined above or R^1 is optionally substituted phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur, or R^1 together with a second R^1 substituent forms a group -O-CH_2-O-, OCH_2CH_2O-, -$CH_2CH_2CH_2$– or -$CH_2CH_2CH_2CH_2$-,

n is 0, 1, 2, 3, 4, 5 or 6;

R^2 is hydrogen, C_{1-6}alkyl, arylC_{1-6} alkyl or together with group P form a 5 to 8 membered ring optionally substituted with one or more C_{1-6}alkyl groups;

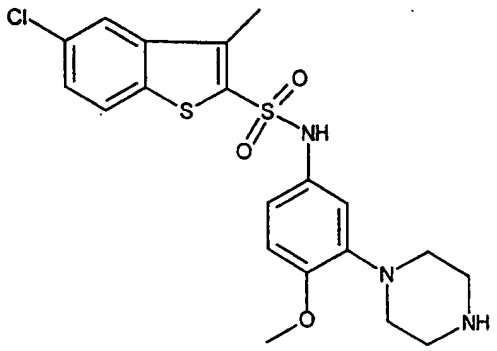
R^3 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy optionally substituted with one or more fluorine atoms, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, , nitro, trifluoromethyl, cyano or aryl or together with the group R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups;

R^4 is -$X(CH_2)p$-R^6 where X is a single bond, CH_2, O, NH or N-alkyl and p is 0 to 6 and R^6 is an optionally substituted 4- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6}alkyl or arylC_{1-6} alkyl; and

R^5 is a group R^3 or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups.

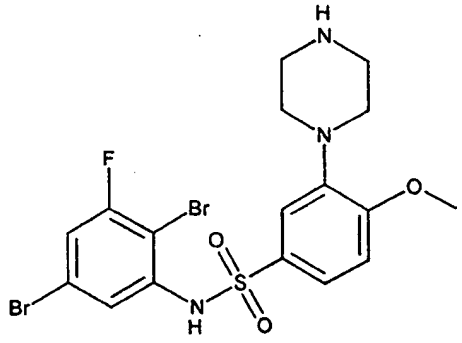
Other compounds for use in this invention include those generically and specifically disclosed in patent application WO 97/27058 (SmithKline Beecham) and European patent applications EP 0815861 (Hoffman-la-Roche) and EP 0930302 (Hoffman-la-Roche).

Particularly preferred compounds of this invention include 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (Example 83 in WO 98/27081), that is to say, the compound of formula (I)



(I)

and *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide (Example 140 in WO 99/02502) that is to say, the compound of formula (II)



(II)

Compounds exhibiting 5-HT_6 receptor antagonist activity may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts of 5-HT_6 receptor antagonists therefore form an aspect of the invention. Suitably, a compound of formula (I) and (II) are used as the hydrochloride salt.

Certain compounds exhibiting 5-HT_6 antagonist activity are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The present invention further provides a method of treatment of ADHD and other related disorders which comprises administering to a host in need thereof an effective amount of a 5-HT_6 receptor antagonist or a pharmaceutically acceptable salt thereof.

When used in therapy, the 5-HT_6 receptor antagonists are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted

for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

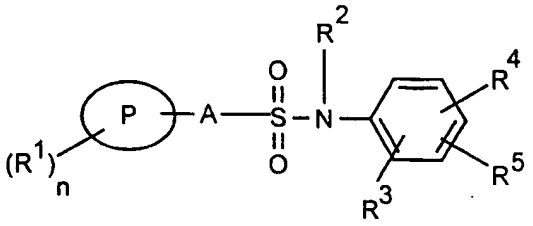
For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

CLAIMS:

1. Use of a compound having 5-HT_6 receptor antagonist activity in the manufacture of a medicament for use in the treatment of ADHD.

2. Use according to claim 1 where the 5-HT_6 receptor antagonist is a compound of formula (A) or a pharmaceutically acceptable salt thereof:



(A)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6,

R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

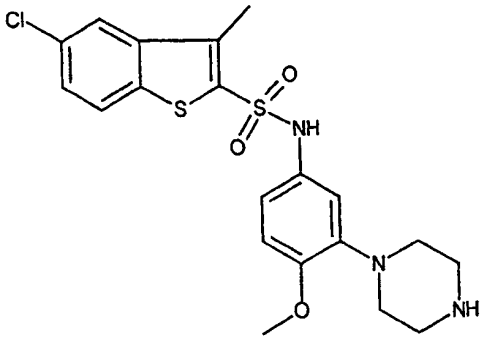
R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is -$X(CH_2)p$-R^6 where X is a single bond, CH_2, O, NH or N- C_{1-6} alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or arylC_{1-6}alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl.

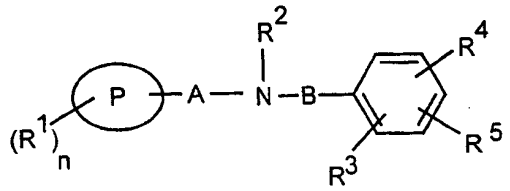
3. Use according to claims 1 and 2 where the 5-HT_6 receptor

antagonist is the compound of formula (I) - 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide or a pharmaceutically acceptable salt thereof.



(I)

4. Use according to claim 1 where the 5-HT_6 receptor antagonist is a compound of formula (B) or a pharmaceutically acceptable salt thereof:



(B)

wherein:

P is phenyl, naphthyl, anthracenyl, a bicyclic heterocyclic ring, a tricyclic heteroaromatic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

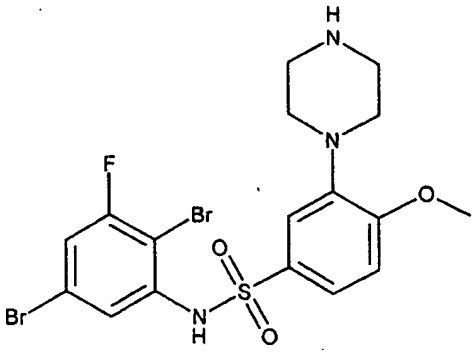
B is SO_2;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more fluorine atoms, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, nitro, cyano, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6}alkyl or optionally substituted phenyl, SR^{11} where R^{11} is as defined above or R^1 is optionally substituted phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur, or R^1 together with a second R^1 substituent forms a group -O-CH_2-O-, OCH_2CH_2O-, -$CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2$-,

n is 0, 1, 2, 3, 4, 5 or 6;

R^2 is hydrogen, C_{1-6}alkyl, arylC_{1-6}alkyl or together with group P form a 5 to 8 membered ring optionally substituted with one or more C_{1-6}alkyl groups;
R^3 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy optionally substituted with one or more fluorine atoms, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, nitro, trifluoromethyl, cyano or aryl or together with the group R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups;
R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N-alkyl and p is 0 to 6 and R^6 is an optionally substituted 4- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or arylC_{1-6} alkyl; and
R^5 is a group R^3 or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups.

5. Use according to claims 1 and 4 where the 5-HT_6 receptor antagonist is the compound of formula (II) - *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide or a pharmaceutically acceptable salt thereof



(II)

6. A pharmaceutical composition for use in the treatment of ADHD which comprises a compound described in any one of claims 2-5 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 99/06218

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 27081 A (SMITHKLINE BEECHAM PLC.) 25 June 1998 (1998-06-25) cited in the application page 1 page 6, line 11 - line 12 see page 27 compound E83 and example 83	6
A	---	1-3
P,X	WO 99 37623 A (SMITHKLINE BEECHAM PLC) 29 July 1999 (1999-07-29) page 1 page 6, line 24	1,4-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2000	20/01/2000

Name and mailing address of the ISA ·	Authorized officer
European Patent Office. P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/06218

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ROGERS D C_(A) J_(A): "Cognitive enhancement effects of the selective 5-HT6 antagonist #SB#- #271046#." BRITISH JOURNAL OF PHARMACOLOGY, 1999, vol. 127, no. proc. suppl., June 1999 (1999-06), page 22p XP000865803 the whole document	6
A	-----	1-3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/06218

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1 relates to a compound defined by reference to a desirable property, namely serotonin "5HT-6 receptor antagonistic activity". The claim covers all compounds having this property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to their pharmacological activity. Again, this lack of clarity in the present is such as to render a meaningful search over the whole of the claimed scope impossible.

Moreover, present claims 2,4,6 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formulas I and II page 5 of the present description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ›nal Application No
PCT/EP 99/06218

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9827081 A	25-06-1998	AU 6090498 A	15-07-1998
		EP 0946539 A	06-10-1999
		NO 993003 A	18-06-1999
WO 9937623 A	29-07-1999	NONE	

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